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Effects of air pollution on the development and progression of digestive diseases: an umbrella review of systematic reviews and meta-analyses

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Abstract

Air pollution, especially particulate matter (PM), is one of the most common risk factors for global burden of disease. However, its effect on the risk of digestive diseases is unclear. Herein, we attempt to explore this issue by reviewing the existing evidence from published meta-analyses. We conducted a systematic literature search to identify all relevant meta-analyses regarding the association of air pollution with digestive diseases, and summarize their major findings. We assessed the methodological quality and evidence quality of the included meta-analyses using the AMSTAR-2 and GRADE tools, respectively, and the overlap of primary studies was assessed by the GROOVE tool. Nine meta-analyses were included in our analysis, containing 43 primary studies with high overlap. In the included meta-analyses, the methodological quality was from critically low to moderate, and the evidence quality was from very low to moderate. The exposure was primarily $PM_{2.5}$. Seven, four, and one meta-analysis investigated the effect of air pollution on liver diseases, gastrointestinal diseases, and pancreatic diseases, respectively. $PM_{2.5}$ exposure was significantly associated with liver dysfunction, chronic liver diseases, liver cancer, and colorectal cancer, but not oesophagus cancer, gastric cancer, or pancreatic cancer. Based on very low to moderate quality evidence from meta-analyses, $PM_{2.5}$ exposure may contribute to the development of some digestive diseases, especially liver diseases.

Keywords Umbrella review, Particulate matter, Liver diseases, Gastrointestinal diseases, Pancreatic diseases

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Introduction

Air pollution is a global challenge and poses a serious threat to human health [1]. According to the Global Burden of Disease (GBD) data, air pollution is one of the major causes of incidence and mortality worldwide [2]. Particulate matter (PM) has become the leading risk factor for the GBD, exceeding high systolic blood pressure and smoking, and contribute to 8.0% of the global total disability-adjusted life years (DALYs). At present, there is clear-cut evidence that air pollution is primarily associated with the risk of respiratory and cardiovascular diseases [3–8]. PM pollution may aggravate oxidative stress, inflammation, and DNA damage in humans, thereby leading to the development and progression of respiratory and cardiovascular diseases [9–12].

Digestive diseases are very common and influence the quality of life and survival. Millions of people worldwide die each year from digestive diseases [13, 14]. Liver cirrhosis is one of the leading causes of incidence and mortality in the world, with more than 1.32 million deaths estimated in 2017 [15], especially in the Asia-Pacific region [16]. The global burden of inflammatory bowel disease (IBD) and non-alcoholic fatty liver disease (NAFLD) is also being dramatically increased [17, 18]. In 2020, colorectal cancer, liver cancer, and gastric cancer were responsible for 940,000, 880,000, and 730,000 deaths, respectively, ranking as the 2nd, 3rd, and 4th leading cancer-related causes globally [19].

Air pollution may cause digestive diseases through various biological mechanisms. Air pollutants can enter the gastrointestinal tract through ciliary clearance, cause intestinal epithelial cell injury, induce oxidative stress, promote the release of proinflammatory factors, and damage intestinal barrier function [20, 21]. They may also cause gut microbiota dysbiosis and further aggravate gastrointestinal inflammation and metabolic abnormalities [22]. Additionally, they may affect liver health through the "gut-liver axis", and increase the risk of liver inflammation, fibrosis, and cancer [23, 24]. Growing epidemiological studies have suggested that air pollution may be associated with the risk of digestive diseases [25–30]. Accordingly, the evidence has been comprehensively synthesized in systematic reviews and meta-analyses. However, the quality of methodology and evidence varied widely among these published systematic reviews and meta-analyses [31], and their findings were different [32, 33]. An umbrella review can systematically evaluate the differences in methodological and evidence quality among systematic reviews and meta-analyses, and synthesize their evidence to ensure the consistency and reliability of the results. To the best of our knowledge, no umbrella review has been performed to evaluate the outcomes of digestive diseases associated with air pollution.

The aim of this study was to provide a comprehensive summary of the findings of meta-analyses and to conduct a systematic assessment of the methodological and evidence quality.

Methods

This umbrella review was conducted in accordance with the Preferred Reporting Items for Overviews of Reviews (PRIOR) guidelines [34] (Supplementary Table 1). The protocol was registered in the PROSPERO database (CRD42024551132).

Search strategy

We used the Medical Subject Heading (MeSH) database to identify common MeSH and Entry Terms about air pollution and digestive diseases to specify our search items. Then, we conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library databases to identify all relevant systematic reviews and meta-analyses regarding the effects of air pollution on the development and progression of digestive diseases, and manually reviewed the reference lists of relevant papers. The last search was performed on June 7, 2024. All search strategies were presented in the Supplementary Table 2.

Selection criteria

Study selection was based on the PEOS (Population, Exposure, Outcome, and Study design) criteria, as follows: (1) population: general population; (2) exposure: common air pollutants, including $PM_{2.5}$, PM_{10}, ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and nitrogen oxides (NO_X); (3) outcome: all types of digestive diseases, including biliary tract diseases, digestive system neoplasms, gastrointestinal diseases, liver diseases, and pancreatic diseases; and (4) study design: systematic reviews and meta-analyses of observational studies, including cohort, case-control, and cross-sectional studies.

The exclusion criteria were as follows: (1) non-human studies or in vitro studies; (2) studies on the effects of some specific conditions, such as occupational exposure, smoking, or passive smoking, on digestive diseases; (3) studies unrelated to the associations of air pollution with digestive diseases; (4) studies without meta-analyses, including systematic reviews without meta-analysis, and (5) meta-analyses where systematic search strategy was unknown or lacking. Publication language was not limited. Two investigators (HZ and SJ) independently screened and included the systematic reviews and meta-analyses by the titles and abstracts and then full-text. Disagreements were resolved by discussing or consultation with another investigator (XQ).

Data extraction

The following information was extracted: first author, publication year, geographic locations of the included primary studies, number of primary studies included, number of individuals included in primary studies, exposures, outcomes of interest, major findings, summary meta-analytic estimates (standardized mean difference, SMD; odds ratio, OR; relative risk, RR; hazard ratio, HR), 95% confidence interval (95%CI), heterogeneity (I^2), and methods used to assess risk of bias and publication bias. The outcomes of interest were determined based on the International Classification of Diseases 11th Revision (ICD-11) (Supplementary Table 3, https://icd.who.int/en). The outcomes of interest included the incidence, mortality, and risk of digestive diseases, with the risk representing a combined summary of incidence and mortality. Heterogeneity was categorized as no significant ($I^2 \leq 25\%$), low ($25\% < I^2 \leq 50\%$), moderate ($50\% < I^2 \leq 75\%$), and high ($I^2 > 75\%$). If meta-analyses focused on multiple exposures or outcomes, we only extracted data related to air pollution and digestive diseases, and ensured that at least two primary studies were included. The data from the finally included meta-analyses were extracted independently by two investigators (HZ and HL), and disagreements were resolved by discussion or consulting with another investigator (XQ).

Overlap of primary studies included in meta-analyses

As previously described [35], we used the Overview Overlapping Graphical Representation (GROOVE) tool to calculate the Corrected Covered Area (CCA) and evaluate the overlap of primary studies among the included meta-analyses [36] (https://doi.org/10.17605/OSF.IO/U2MS4). We also assessed the overlap of primary studies among the included meta-analyses with coincident exposures and outcomes. The CCA was classified as follows: 0–5% indicated light overlap, 6–10% moderate overlap, 11–15% high overlap, and more than 15% very high overlap. Primary studies included in meta-analyses were extracted independently by two investigators (HZ and PX), and disagreements were resolved by discussion or consultation with another investigator (XQ).

Synthesis of evidence from included in meta-analyses

We summarized the characteristics of the included meta-analyses, including first author, publication year, number of primary studies included, number of individuals and geographic locations included in primary studies, study design, exposures, outcomes of interest, and major findings. To describe the distribution of effect estimates, the statistical results from the meta-analyses, including pooled effect estimates, 95%CI, and heterogeneity, were grouped according to the type of diseases (i.e., liver diseases, gastrointestinal diseases, and pancreatic diseases), and visually represented as forest plot (Fig. 1, R software-4.4.2, https://cloud.r-project.org/bin/windows/base/). The OR, RR, and HR were converted to the percentage excess risk [excess risk % =(OR/HR/RR-1)×100].

Methodological quality of the included meta-analyses

As previously described [37], we used the Assessment of Multiple meta-analyses two (AMSTAR-2) tool to assess the methodological quality of the included meta-analyses [38] (http://links.lww.com/JS9/B194). It contained seven critical questions and nine non-critical questions that should be answered as "yes", "partly yes", and "no". Overall confidence in the results of the meta-analyses was categorized as "high" for none or one non-critical weakness, "moderate" for more than one non-critical weakness without critical weaknesses, "low" for one critical weakness, and "critically low" for more than one critical weakness. The methodological quality of the included meta-analyses was evaluated independently by two investigators (HZ and XW), and disagreements were resolved by discussion or consultation with another investigator (XQ).

Evidence quality of the included meta-analyses

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tool to assess the evidence quality from the included meta-analyses [39] (https://gdt.gradepro.org/app/handbook/handbook.html). Because all included meta-analyses were observational, the evidence quality had to be initially rated as low. The evidence quality was assessed by five downgrade criteria and three upgrade criteria. The downgrade criteria were as follows: (1) Risk of bias, which was defined as being rated as high or not being assessed; (2) inconsistency, which was defined as heterogeneity more than 50% according to the results of a meta-analysis; (3) indirectness, which was defined as significant differences between the meta-analysis review question and the PEO of the primary study; (4) imprecision, which was defined as effect estimates that were not statistically significant according to the results of a meta-analysis; and (5) publication bias, which was defined as the original meta-analysis found that publication bias or without evaluation. The upgrade criteria were as follows: (1) large magnitude of effect, which was defined as either a 200% increase in excess risk or a 50% reduction, according to the results of meta-analyses; (2) plausible confounding, which was defined as all plausible residual confounding was corrected; and (3) dose-response gradient, which was defined as the level of air pollution exposure associated with the risk

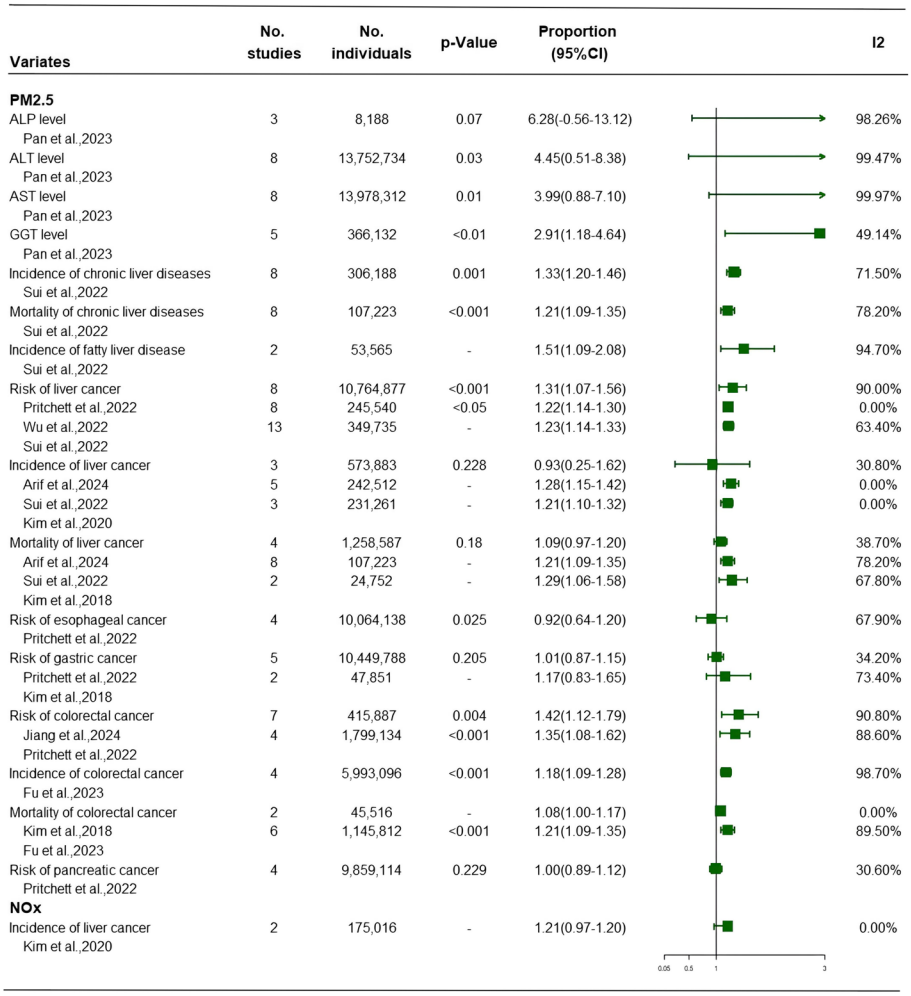


Fig. 1 Forest plot of effect estimates of the included meta-analyses

of digestive diseases. The evidence quality from meta-analyses was graded as high, moderate, low, or very low, and was independently evaluated by two investigators (HZ and XW). Disagreements were resolved by discussion or consulting with another investigator (XQ).

Results

Study selection

Overall, 529 records were initially screened. After excluding 56 duplicate records, 444 records were excluded upon reviewing titles and abstracts. Subsequently, 29 articles were assessed in full texts, of which nine were included [32, 40–47] (Fig. 2). The list of excluded records was reported in the Supplementary Excel File 1.

Characteristics of primary studies included in meta-analyses

The meta-analyses included in our umbrella review were published during a period from 2015 to 2024, recruiting 43 primary studies (Supplementary Table 4). The overall overlap of primary studies was high (CCA = 13.08%) (Fig. 3). All of them examined the effects of air pollution on digestive diseases in multiple regions of the world. These primary studies were mainly conducted in Asia ($n = 20$, 46.51%), Europe ($n = 9$, 20.93%), North America ($n = 12$, 27.91%), and South America ($n = 2$, 4.65%). Most of the primary studies were cohort studies ($n = 33$, 78.57%).

Characteristics of the included meta-analyses

The included meta-analyses investigated the effect of different air pollutant exposures on digestive diseases (Table 1). All of them provided the effect estimates of continuous variables of air pollutants on digestive diseases. The exposure was primarily $PM_{2.5}$ (n = 9, 100.00%) and NO_X ($n = 1$, 11.11%). However, other air pollutants have not been investigated yet. The outcomes covered the risk, incidence, and mortality of liver diseases,

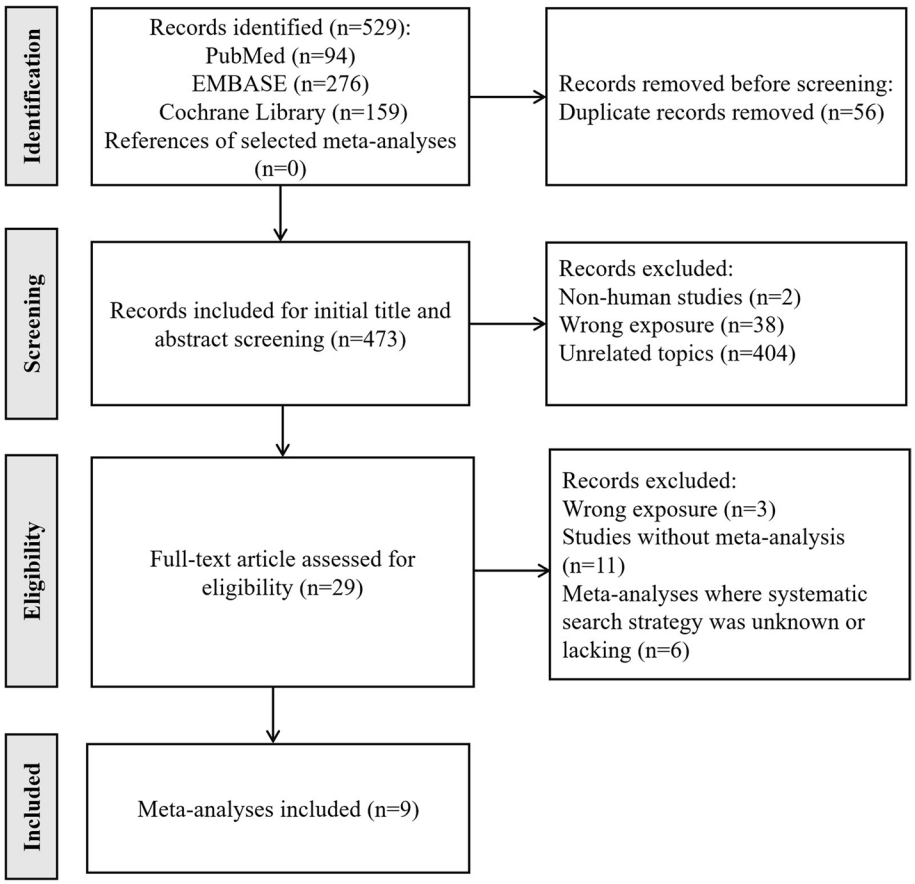


Fig. 2 Flow chart of study selection

gastrointestinal diseases, and pancreatic diseases. The meta-analyses recruited at least two primary studies.

Methodological quality of the included meta-analyses

For the critical questions, two of the included meta-analyses had their prior protocols published [41, 46] (Q2); seven performed a comprehensive literature search [32, 40–44, 46] (Q4); one provided a list of excluded studies [41] (Q7); one performed an appropriate approach for assessing the risk of bias [41] (Q9); all of them employed satisfactory statistical methods for data synthesis (Q11); four accounted for the risk of bias in primary studies in the "Discussion" section. [41] (Q13); and eight adequately investigated the publication bias and discussed its possible impact on the results [32, 40–44, 46, 47] (Q15). For the non-critical questions, all of them included population, intervention, and outcomes (Q1); two explained their study designs for inclusion criteria [45, 47] (Q3); six carried out study selection in duplicate [32, 41–45] (Q5); six carried out data extraction in duplicate [32, 41–45] (Q6); all of them described their included primary studies in details (Q8); three reported the sources of funding [43, 45, 47] (Q10); one assessed the potential impact of risk of bias on the outcomes [41] (Q12); eight reported the possible causes of heterogeneity and discussed the impact [32, 40–43, 45–47] (Q14); and all of them claimed no conflict of interest (Q16). Generally, one included meta-analysis was of moderate quality [41], and eight were of critically low quality [32, 40, 42–47] (Table 2).

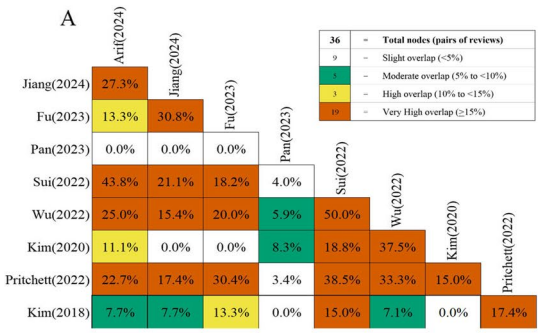
Liver diseases

Seven meta-analyses investigated the effect of air pollution on liver diseases [32, 40–44, 47], including the association of $PM_{2.5}$ exposure with liver dysfunction ($n=1$), chronic liver diseases ($n=1$), and liver cancer ($n=6$), as well as the association of NO_x exposure with liver cancer ($n=1$) (Table 1).

Liver dysfunction

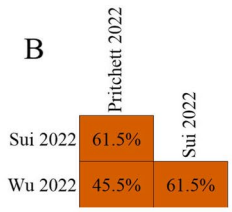
One meta-analysis [42], including 10 primary studies with more than 14 million individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was significantly

A



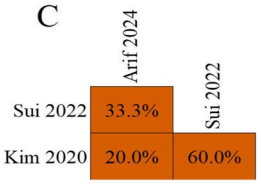
Number of columns (number of reviews)	c	9
Number of rows (number of index publications)	r	43
Number of included primary studies (including double counting)	N	88
Covered area	N/(rc)	22.74%
Corrected covered area	(N-r)/(rc-r)	13.08%
Interpretation of overlap	**High overlap**	
Structural Zeros	X	0
Corrected covered area (adjusting by structural zeros)	(N-r)/(rc-r-X)	13.08%

B



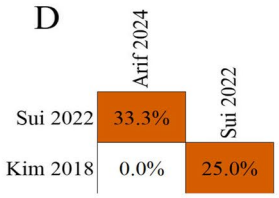
Number of columns (number of reviews)	c	3
Number of rows (number of index publications)	r	13
Number of included primary studies (including double counting)	N	29
Covered area	N/(rc)	74.36%
Corrected covered area	(N-r)/(rc-r)	61.54%
Interpretation of overlap	**Very High overlap**	
Structural Zeros	X	0
Corrected covered area (adjusting by structural zeros)	(N-r)/(rc-r-X)	61.54%

C



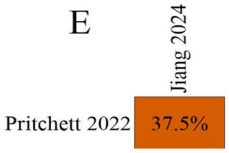
Number of columns (number of reviews)	c	3
Number of rows (number of index publications)	r	6
Number of included primary studies (including double counting)	N	11
Covered area	N/(rc)	61.11%
Corrected covered area	(N-r)/(rc-r)	41.67%
Interpretation of overlap	**Very High overlap**	
Structural Zeros	X	0
Corrected covered area (adjusting by structural zeros)	(N-r)/(rc-r-X)	41.67%

D



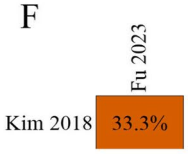
Number of columns (number of reviews)	c	3
Number of rows (number of index publications)	r	9
Number of included primary studies (including double counting)	N	14
Covered area	N/(rc)	51.85%
Corrected covered area	(N-r)/(rc-r)	27.78%
Interpretation of overlap	**Very High overlap**	
Structural Zeros	X	0
Corrected covered area (adjusting by structural zeros)	(N-r)/(rc-r-X)	27.78%

E



Number of columns (number of reviews)	c	2
Number of rows (number of index publications)	r	8
Number of included primary studies (including double counting)	N	11
Covered area	N/(rc)	68.75%
Corrected covered area	(N-r)/(rc-r)	37.50%
Interpretation of overlap	**Very High overlap**	
Structural Zeros	X	0
Corrected covered area (adjusting by structural zeros)	(N-r)/(rc-r-X)	37.50%

F



Number of columns (number of reviews)	c	2
Number of rows (number of index publications)	r	6
Number of included primary studies (including double counting)	N	8
Covered area	N/(rc)	66.67%
Corrected covered area	(N-r)/(rc-r)	33.33%
Interpretation of overlap	**Very High overlap**	
Structural Zeros	X	0
Corrected covered area (adjusting by structural zeros)	(N-r)/(rc-r-X)	33.33%

Fig. 3 Overlap heat map of the primary studies included in the meta-analyses. **A** Overall primary studies; **B** Risk of liver cancer; **C** Incidence of liver cancer; **D** Mortality of liver cancer; **E** Risk of colorectal cancer; **F** Mortality of colorectal cancer

Table 1 Major characteristics and findings of these included meta-analyses

First author (year)	Number of included primary studies/ individuals	Geographic locations	Study design	Risk of bias assessment	Publication bias assessment	Statistical model	Exposure(s)	Outcome(s) of interest	Major findings
Arif (2024) [47]	7/ >1,830,000	1 in Asia, 2 in Europe, 3 in North America, 1 in South America	7 cohorts	NA	Egger's test	REM	$PM_{2.5}$	Incidence of liver cancer; Mortality of liver cancer	Exposure to $PM_{2.5}$ was not associated with increased incidence or mortality of liver cancer.
Jiang (2024) [45]	7/ 415,887	2 in Asia, 1 in Europe, 3 in North America, 1 in South America	7 cohorts	NA	NA	REM	$PM_{2.5}$	Risk of colorectal cancer	The joint exposure to $PM_{2.5}$ was associated with increased risk of colorectal cancer.
Fu (2023) [46]	10/ 7,138,908	6 in Asia, 4 in North America	7 cohorts, 1 case-control, 1 time-series, 1 spatial and temporal ecological	NA	Egger's test and Begg's test	REM/FEM	$PM_{2.5}$	Incidence of colorectal cancer; Mortality of colorectal cancer	Exposure to $PM_{2.5}$ was associated with increased incidence and mortality of colorectal cancer.
Pan (2023) [42]	10/ 14,000,449	8 in Asia, 1 in Europe, 1 in North America	5 cohorts, 2 cross-sectional, 2 longitudinal, 1 time-series	NA	Begg funnel plots and Egger's test	REM	$PM_{2.5}$	Changes in liver enzyme levels	Increments in $PM_{2.5}$ exposure were associated with higher level of ALT, AST, and GGT.
Sui (2022) [32]	16/ 331,114	7 in Asia, 3 in Europe, 5 in North America, 1 in South America	15 cohorts, 1 cross-sectional	NA	Begg's funnel plot and Egger's test	REM/FEM	$PM_{2.5}$	Risk of chronic liver diseases	Long-term exposure to $PM_{2.5}$ was associated with increased risk of chronic liver disease.
Wu (2022) [40]	8/ 245,540	4 in Asia, 1 in Europe, 3 in North America	7 cohorts, 1 spatial and temporal ecological	NA	Egger's test and Begg's test	FEM	$PM_{2.5}$	Risk of HCC	Exposure to $PM_{2.5}$ was significantly associated with increased risk of HCC.
Kim (2020) [43]	3/ 231,261	1 in Asia, 1 in Europe, 1 in North America	3 cohorts	NA	Begg's funnel plot and Egger's test	REM	$PM_{2.5}$ NOx	Incidence of liver cancer	Long-term exposure to $PM_{2.5}$, but not ^{NOx}, may increase the incidence of liver cancer.

Table 1 (continued)

First author (year)	Number of included primary studies/ individuals	Geographic locations	Study design	Risk of bias assessment	Publication bias assessment	Statistical model	Exposure(s)	Outcome(s) of interest	Major findings
Pritchett (2022) [41]	20/ >403,110,000	7 in Asia, 6 in Europe, 7 in North America	18 cohorts, 1 case-control, 1 time-series	Cochrane Collaboration's risk of bias tool and Agency for Health care Research and Quality's domains	Begg's funnel plot and Egger's test	REM	$PM_{2.5}$	Risk of stomach cancer; Risk of colorectal cancer; Risk of oesophagus cancer; Risk of liver cancer; Risk of pancreatic cancer	Exposure to $PM_{2.5}$ was associated with increased risk of colorectal cancers and liver cancer, but not stomach cancer, esophagus cancer, and pancreatic cancer.
Kim (2018) [44]	7/ 326,161	2 in Asia, 2 in Europe, 3 in North America	7 cohorts	NA	Begg funnel plots and Egger's test	REM	$PM_{2.5}$	Mortality of liver cancer; Mortality of gastric cancer; Mortality of colorectal cancer	Exposure to $PM_{2.5}$ was associated with increased mortality of liver cancer and colorectal cancer, but not gastric cancer.

Abbreviations: *NA* Not applicable, *FEM* Fixed effect model, *REM* Random effects model, *PM* Particulate matter, *HCC* Hepatocellular carcinoma, NO_x Nitrogen oxides

Table 2 Methodological quality of these included meta-analyses by AMSTAR-2

First author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	No. critical weaknesses	Quality
Arif (2024) [47]	Y	PY	Y	PY	N	N	N	Y	N	Y	Y	N	N	Y	Y	Y	5	Critically low
Jiang (2024) [45]	Y	N	Y	PY	Y	Y	N	Y	N	Y	Y	N	N	Y	N	Y	6	Critically low
Fu (2023) [46]	Y	Y	N	Y	N	N	N	Y	N	N	Y	N	N	Y	Y	Y	3	Critically low
Pan (2023) [42]	Y	N	N	Y	Y	Y	N	Y	N	N	Y	N	N	Y	Y	Y	4	Critically low
Sui (2022) [32]	Y	N	N	Y	Y	Y	N	Y	N	N	Y	N	N	Y	Y	Y	4	Critically low
Wu (2022) [40]	Y	N	N	Y	N	N	N	Y	N	N	Y	N	N	Y	Y	Y	4	Critically low
Kim (2020) [43]	Y	N	N	Y	Y	Y	N	Y	N	Y	Y	N	N	Y	Y	Y	4	Critically low
Pritchett (2022) [41]	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	0	Moderate
Kim (2018) [44]	Y	N	N	Y	Y	Y	N	Y	N	N	Y	N	N	PY	Y	Y	4	Critically low

Q1. Research questions and inclusion criteria for the meta-analyses include population, intervention, comparator group, and outcome

Q2. The research protocol was announced before the study

Q3. Explained study design for inclusion criteria

Q4. Comprehensive literature search strategy

Q5. Performed study selection in duplicate

Q6. Performed data extraction in duplicate

Q7. Provide a list of excluded studies and justify

Q8. Included studies described in adequate detail

Q9. Performed an appropriate approach for assessing the risk of bias

Q10. Reported on the sources of funding for studies

Q11. Performed satisfactory statistical methods for data synthesis

Q12. Assessed the potential impact of risk of bias on study outcomes in individual studies

Q13. Accounted for risk of bias in individual studies in the "Discussion" section interpreting results

Q14. Reported the possible causes of heterogeneity and discussed

Q15. Investigated publication bias

Q16. Reported conflict of interest

Questions Q2, Q4, Q7, Q9, Q11, Q13, and Q15 were considered critical questions

Abbreviations: *AMSTAR* Assessment of Multiple Systematic Reviews, *Y* Yes, *PY* Partial yes, *N* No

positively associated with elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT), but not alkaline phosphatase. For every increase of 10 μg/m³ in $PM_{2.5}$ concentration, the levels of ALT, AST, and GGT increased by 4.45% ($P=0.03$, $I^2=99.47\%$), 3.99% ($P=0.01$, $I^2=99.97\%$), and 2.91% ($P<0.001$, $I^2=49.14\%$), respectively (Table 3).

Chronic liver diseases

One meta-analysis [32], including 16 primary studies with more than 330,000 individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was significantly positively associated with the incidence and mortality of chronic liver disease, especially fatty liver disease. For every increase of 10 μg/m³ in $PM_{2.5}$ concentration, the incidence and mortality of chronic liver diseases increased by 33% (95%CI: 1.20–1.46, $I^2=71.50\%$) and 21% (95%CI: 1.09–1.35, $I^2=78.20\%$), respectively. For every increase of 10 μg/m³ in $PM_{2.5}$ concentration, the incidence of fatty liver disease increased by 51% (95%CI: 1.09–2.08, $I^2=94.70\%$) (Table 3).

Liver cancer

$PM_{2.5}$: Three meta-analyses [32, 40, 41], including 13 primary studies with more than 12.83 million individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was significantly positively associated with the risk of liver cancer. Two meta-analyses [32, 43], including six primary studies with more than 9.33 million individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was significantly positively associated with the incidence of liver cancer, but another meta-analysis [47], including three primary studies with more than 590,000 individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was not significantly associated with the incidence of liver cancer. Three meta-analyses [32, 44, 47], including nine primary studies with more than 12.24 million individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was positively associated with the mortality of liver cancer, but this association was not statistically significant in one of them [47]. For every increase of 10 μg/m³ in $PM_{2.5}$ concentration, the risk, incidence, and mortality of liver cancer increased by 22% (95%CI: 1.14–1.30, $I^2=0.00\%$) to

Table 3 Quality of evidence in these included meta-analyses by GRADE

Exposure	Outcomes	First author (year)	Number of included primary studies/ individuals	Effect estimates (95%CIs)	*P*-value	I^2	Certainty assessment						Quality of evidence
							Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	
Liver enzyme levels													
$PM_{2.5}$ per 10 μg/m^3	ALP levels	Pan (2023) [42]	3/ 8,188	SMD: 6.28 (−0.56, 13.12)	0.07	98.26%	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	ALT levels	Pan (2023) [42]	8/ 13,752,734	SMD: 4.45 (0.51, 8.38)	0.03	99.47%	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	AST levels	Pan (2023) [42]	8/ 13,978,312	SMD: 3.99 (0.88, 7.10)	0.01	99.97%	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	GGT levels	Pan (2023) [42]	5/ 366,132	SMD: 2.91 (1.18, 4.64)	< 0.01	49.14%	Serious[a]	Not serious	Not serious	Not serious	Not serious	Dose-response gradient.	Low
Chronic liver diseases													
$PM_{2.5}$ per 10 μg/m^3	Incidence	Sui (2022) [32]	8/ 306,188	HR: 1.33 (1.20, 1.46)	0.001	71.50%	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	Mortality	Sui (2022) [32]	8/ 107,223	HR: 1.21 (1.09, 1.35)	< 0.001	78.20%	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Very low
Fatty liver disease													
$PM_{2.5}$ per 10 μg/m^3	Incidence	Sui (2022) [32]	2/ 53,565	HR: 1.51 (1.09, 2.08)	NA	94.70%	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Very low
Liver cancer													
$PM_{2.5}$ per 10 μg/m^3	Risk	Pritchett (2022) [41]	8/ > 10,764,877	RR: 1.31 (1.07, 1.56)	< 0.001	90.00%	Not serious	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Moderate
$PM_{2.5}$ per 10 μg/m^3	Risk	Wu (2022) [40]	8/ 245,540	HR: 1.22 (1.14, 1.30)	< 0.05	0.00%	Serious[a]	Not serious	Not serious	Not serious	Not serious	Dose-response gradient.	Low
$PM_{2.5}$ per 10 μg/m^3	Risk	Sui (2022) [32]	13/ 349,735	HR: 1.23 (1.14, 1.33)	NA	63.40%	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	Incidence	Arif (2024) [47]	3/ 573,883	RR: 0.93 (0.25,1.62)	0.228	30.80%	Serious[a]	Not serious	Not serious	Serious[c]	Serious[d]	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	Incidence	Sui (2022) [32]	5/ 242,512	HR: 1.28 (1.15, 1.42)	NA	0.00%	Serious[a]	Not serious	Not serious	Not serious	Not serious	Dose-response gradient.	Low

Table 3 (continued)

Exposure	Outcomes	First author (year)	Number of included primary studies/ individuals	Effect estimates (95%CIs)	*P*-value	I^2	Certainty assessment						Quality of evidence
							Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	
$PM_{2.5}$ per 10 μg/m^3	Incidence	Kim (2020) [43]	3/ 231,261	RR: 1.21 (1.10, 1.32)	NA	0.00%	Serious[a]	Not serious	Not serious	Not serious	Not serious	Dose-response gradient.	Low
NO_x per 10 μg/m^3	Incidence	Kim (2020) [43]	2/ 175,016	RR: 1.21 (0.97, 1.16)	NA	0.00%	Serious[a]	Not serious	Not serious	Serious[c]	Not serious	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	Mortality	Arif (2024) [47]	4/ > 1,258,587	RR: 1.09 (0.97, 1.20)	0.180	38.70%	Serious[a]	Not serious	Not serious	Serious[c]	Serious[d]	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	Mortality	Sui (2022) [32]	8/ 107,223	HR: 1.21 (1.09, 1.35)	NA	78.20%	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	Mortality	Kim (2018) [44]	2/ 24,752	RR: 1.29 (1.06, 1.58)	NA	67.80%	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Very low
Esophageal cancer													
$PM_{2.5}$ per 10 μg/m^3	Risk	Pritchett (2022) [41]	4/ > 10,064,138	RR: 0.92 (0.64, 1.20)	0.025	67.90%	Not serious	Serious[b]	Not serious	Serious[c]	Not serious	Dose-response gradient.	Very low
Gastric cancer													
$PM_{2.5}$ per 10 μg/m^3	Risk	Pritchett (2022) [41]	5/ > 10,449,788	RR: 1.01 (0.87, 1.15)	0.205	34.20%	Not serious	Not serious	Not serious	Serious[c]	Serious[d]	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	Mortality	Kim (2018) [44]	2/ 47,851	RR: 1.17 (0.83, 1.65)	NA	73.40%	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious	Dose-response gradient.	Very low
Colorectal cancer													
$PM_{2.5}$ per 10 μg/m^3	Risk	Jiang (2024) [45]	7/ 415,887	RR: 1.42 (1.12, 1.79)	0.004	90.80%	Serious[a]	Serious[b]	Not serious	Not serious	Serious[d]	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	Risk	Pritchett (2022) [41]	4/ 1,799,134	RR: 1.35 (1.08, 1.62)	< 0.001	88.60%	Not serious	Serious[b]	Not serious	Not serious	Serious[d]	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	Incidence	Fu (2023) [46]	4/ 5,993,096	OR: 1.18 (1.09, 1.28)	< 0.001	98.70%	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Very low
$PM_{2.5}$ per 10 μg/m^3	Mortality	Fu (2023) [46]	6/ 1,145,812	OR: 1.21 (1.09, 1.35)	< 0.001	89.50%	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Dose-response gradient.	Very low

Table 3 (continued)

Exposure	Outcomes	First author (year)	Number of included primary studies/ individuals	Effect estimates (95%CIs)	*P*-value	I^2	Certainty assessment						Quality of evidence
							Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	
$PM_{2.5}$ per 10 μg/m^3	Mortality	Kim (2018) [44]	2/ 45,516	RR: 1.08 (1.00, 1.17)	NA	0.00%	Serious[a]	Not serious	Not serious	Not serious	Not serious	Dose-response gradient.	Low
Pancreatic cancer													
$PM_{2.5}$ per 10 μg/m^3	Risk	Pritchett (2022) [41]	4/ 9,859,114	RR: 1.00 (0.89, 1.12)	0.229	30.60%	Not serious	Not serious	Not serious	Serious[c]	Serious[d]	Dose-response gradient.	Very low

Effect estimates included SMD, OR, RR, and HR

Abbreviations: *95%CI* 95% confidence interva, I^2Heterogeneity, *SMD* Standardized mean difference, *OR* Odds ratio, *RR* Relative risk, *HR* Hazard ratio, *NA* Not applicable, *PM* Particulate matter, *AKP* Alkaline phosphatase, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *GGT* Gamma-glutamyl transferase, NO_x Nitrogen oxides

[a] Risk of bias would be considered serious, if it was rated as high risk or not assessed

[b] Inconsistency would be considered serious, if the I^2 was more than 50% according to the results of a meta-analysis

[c] Imprecision would be considered serious, if the effect estimates were not statistically significant

[d] Publication bias would be considered serious, if it was serious according to the original meta-analysis or was not evaluated by the original meta-analysis

31% (95%CI: 1.07–1.56, $I^2=90.00\%$), 21% (95%CI: 1.10–1.32, $I^2=0.00\%$) to 28% (95% CI: 1.15–1.42, $I^2=0.00\%$), and 9% (95%CI: 0.97–1.20, $I^2=38.70\%$) to 29% (95%CI: 1.06–1.58, $I^2=67.80\%$), respectively (Table 3). The overlap of primary studies investigating the association of $PM_{2.5}$ exposure with the risk, incidence, and mortality of liver cancer was very high, with CCA of 61.54%, 41.67%, and 27.78%, respectively (Fig. 3).

NO_x: One meta-analysis [43], including two primary studies with more than 170,000 individuals (Supplementary Table 4), suggested that NO_x exposure was positively associated with the incidence of liver cancer, but this association was not statistically significant (Table 3).

Gastrointestinal diseases

Four meta-analyses investigated the effect of air pollution on gastrointestinal diseases [41, 44–46], including the association of $PM_{2.5}$ exposure with oesophagus cancer (n = 1), gastric cancer (n = 2), and colorectal cancer (n = 4) (Table 1).

Oesophagus cancer

One meta-analysis [41], including four primary studies with more than 1.25 million individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was negatively associated with the risk of oesophagus cancer, but this association was not statistically significant (Table 3).

Gastric cancer

One meta-analysis [41], including five primary studies with more than 10.6 million individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was positively associated with the risk of gastric cancer, but this association was not statistically significant. One meta-analysis [44], including two primary studies with more than 700,000 individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was positively associated with the mortality of gastric cancer, but this association was also not statistically significant (Table 3).

Colorectal cancer

Two meta-analyses [41, 45], including eight primary studies with more than 11.99 million individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was significantly positively associated with the risk of colorectal cancer. One meta-analysis [46], including four primary studies with more than 5.99 million individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was significantly positively associated with the incidence of colorectal cancer. Two meta-analyses [44, 46], including six primary studies with more than 1.72 million individuals (Supplementary Table 4), suggested that $PM_{2.5}$ exposure was significantly positively associated with the mortality of colorectal cancer. For every increase of 10 $\mu g/m^3$ in $PM_{2.5}$ concentration, the risk, incidence, and mortality of colorectal cancer increased by 35% (95%CI: 1.08–1.62, $I^2=88.60\%$) to 42% (95%CI: 1.12–1.79, $I^2=90.80\%$), 18% (95%CI: 1.09–1.28, $I^2=98.70\%$), and 8% (95%CI: 1.00–1.17, $I^2=0.00\%$) to 21% (95%CI: 1.09–1.35, $I^2=89.50\%$), respectively (Table 3). The overlap of primary studies investigating the association of $PM_{2.5}$ exposure with the risk and mortality of colorectal cancer was very high, with CCA of 37.50% and 33.33%, respectively (Fig. 3).

Pancreatic diseases

One meta-analysis [41], including four primary studies with more than 10.01 million individuals (Supplementary Table 4), did not demonstrate any significant association between $PM_{2.5}$ exposure and the risk of pancreatic cancer (Table 3).

Evidence quality of the included meta-analyses

We assessed the evidence quality of 26 pieces of evidence for 18 outcomes from nine meta-analyses. For the downgrade criteria, the risk of bias was found in 21 pieces of evidence from eight meta-analyses [32, 40, 42–47]; the inconsistency was found in 15 pieces of evidence from six meta-analyses [32, 41, 42, 44–46]; the indirectness was not found in all the evidence from nine meta-analyses; the imprecision was found in eight pieces of evidence from five meta-analyses [41–44, 47]; and the publication bias was found in six pieces of evidence from three meta-analyses [41, 45, 47]. For the upgrade criteria, the large magnitude of effect was not found in all meta-analyses; the plausible confounding has been adjusted in all primary studies from the included meta-analyses, but the adjusted factors were inconsistent among them; and the dose-response gradient was found in all meta-analyses. Among the meta-analyses on liver diseases, the evidence quality was very low to low for liver dysfunction ($n=4$), low for chronic liver disease ($n=2$) and fatty liver disease ($n=1$), and very low to moderate for liver cancer ($n=10$). Among the meta-analyses on gastrointestinal diseases, the evidence quality was very low for oesophagus cancer ($n=1$) and gastric cancer ($n=7$), and very low to low for colorectal cancer ($n=5$). Among the meta-analyses on pancreatic diseases, the evidence quality was very low for pancreatic cancer ($n=1$) (Table 3).

Discussion

In this umbrella review, we summarized the evidence of the association between exposure to air pollution and different digestive diseases. In the meta-analyses we included, $PM_{2.5}$ was the most extensively investigated

exposure. In comparison, the evidence from meta-analyses on the effects of other air pollutants on digestive diseases remains insufficient. Additionally, liver diseases (chronic liver disease, liver dysfunction, liver cancer), gastrointestinal diseases (oesophagus cancer, gastric cancer, colorectal cancer), and pancreatic diseases (pancreatic cancer) have been investigated, while biliary diseases have not been studied.

Based on the current meta-analyses, $PM_{2.5}$ exposure was significantly associated with some liver diseases. Very low to low-quality evidence suggested $PM_{2.5}$ exposure was positively associated with liver dysfunction, and very low-quality evidence suggested $PM_{2.5}$ exposure was positively associated with chronic liver diseases, especially fatty liver disease. However, the evidence for the association between air pollution and liver cancer was inconsistent. Specifically, low- to moderate-quality evidence suggested $PM_{2.5}$ exposure was positively associated with liver cancer, but very low-quality evidence suggested that NO_x and $PM_{2.5}$ were not statistically significant association with liver cancer. According to the evidence quality, $PM_{2.5}$ exposure may be positively associated with liver cancer. Another published systematic review also indicated that $PM_{2.5}$ exposure was associated with the mortality of liver cancer [33].

Limited evidence has investigated the association between $PM_{2.5}$ exposure and gastrointestinal and pancreatic diseases. Very low to low-quality evidence suggested $PM_{2.5}$ exposure was positively associated with colorectal cancer. However, very low-quality evidence suggested that $PM_{2.5}$ exposure was not statistically significantly associated with oesophagus cancer, gastric cancer, or pancreatic cancer.

$PM_{2.5}$ can enter the gastrointestinal tract through the process of digestion and absorption, or enter the blood circulation in a number of ways to reach other tissues or organs, posing a threat to digestive diseases [20, 48]. Potential mechanisms of digestive diseases associated with $PM_{2.5}$ exposure include inflammation, oxidative stress, immunity, metabolic disorder, and DNA damage [49].

The liver, as the main organ of detoxification metabolism, is the most seriously affected by $PM_{2.5}$[50]. Firstly, exposure to $PM_{2.5}$ can lead to increased reactive oxygen species (ROS) production, causing oxidative stress and then local or systemic inflammation which prompts the release of inflammatory factors [51, 52]. An animal study has shown that exposure to $PM_{2.5}$ can cause liver dysfunction through inflammation and oxidative stress [53]. In addition, inflammation and oxidative stress in the liver also disrupt lipid metabolism, potentially causing the development of NAFLD [54]. Studies have reported that $PM_{2.5}$ can disrupt hepatic cholesterol and bile acid metabolism through key signaling pathways such as LCAT-CE and CYP7A1 [55], which may be associated with the risk of liver cancer [56]. $PM_{2.5}$ can also activate PINK1/Parkin signaling pathway to trigger mitophagy, inducing the activation of hepatic stellate cells (HSCs) and promoting liver fibrosis, which provided a basis for the development of liver cancer [57]. Notably, $PM_{2.5}$ can stimulate the overexpression of transforming growth factor-β1 (TGF-β1) in liver cells [58]. Overexpression of TGF-β1 can inhibit the function of T cells and natural killer cells, leading to immune escape, which is particularly important in cancer progression [59]. Moreover, $PM_{2.5}$ can damage DNA structure and function by inducing oxidative stress, changing DNA methylation, and inhibiting DNA repair, thereby promoting the prevalence and progression of liver cancer [60–62].

$PM_{2.5}$ can be exposed to the colon and rectum through various pathways, which may increase the risk of colorectal cancer [63, 64]. $PM_{2.5}$ exposure can trigger intestinal inflammation through the vascular endothelial growth factor (VEGF) receptor signaling pathway [65, 66], and promote tumor cell proliferation and immune escape through COX-2 and its metabolites, such as prostaglandin E2 [67, 68]. $PM_{2.5}$ can also induce gut microbiota dysbiosis, which may exacerbate intestinal inflammation and abnormal lipid metabolism [69, 70]. In addition, $PM_{2.5}$ can trigger oxidative stress in the colon and rectum by inducing the production of ROS, thereby leading to DNA damage and gene mutations and interfering with DNA modification and repair, finally accelerating colorectal cancer progression [71–74].

According to the AMSTAR-2 tool, the methodological quality of the included meta-analyses was unsatisfactory. This was mainly because prior protocols, explanations of study design, comprehensive and transparent literature searches, repeated study selection and data extraction, lists and justifications for excluded studies, reporting of funding sources, and/or assessment and discussion of risk of bias were lacking. According to the GRADE tool, most of the evidence was of very low or low quality, and only one was of moderate quality, which suggested some limitations of the included meta-analyses. First, the methodological quality of the included meta-analyses was unsatisfactory, which directly affected the quality of overall evidence. Second, the moderate-to-high heterogeneity observed in the included meta-analyses can be attributed to the differences in study design, exposure assessment methods, geographic locations, and control of confounding variables among the primary studies, which may reduce the reliability and statistical power of the evidence and increase the difficulty of interpretation of outcomes. Finally, potential publication bias was not

adequately assessed or discussed in several meta-analyses, further weakening the robustness of the evidence.

This umbrella review should be the first to explore the association between different digestive diseases and air pollution, providing an overview of the differences in the effects of air pollution on various digestive diseases. Additionally, we identified the digestive diseases that were potentially more susceptible to air pollution, providing valuable insights for future study, and filling the gaps in the existing evidence. Of course, our study has some limitations. First, we included only published studies, and systematic reviews without meta-analyses were excluded, which may lead to selection bias. Second, our evidence primarily came from Asia, Europe, North America, and South America, but not Oceania or Africa, which may affect the generalizability of the evidence. Last, the overlap of the primary studies included in these meta-analyses was high. Some primary studies investigating liver cancer and colorectal cancer were included in duplicate across multiple meta-analyses, potentially leading to overconfidence in the relevant outcomes.

Despite numerous evidence to support the effects of air pollution on digestive diseases, gaps remain. The majority of evidence has concentrated on $PM_{2.5}$, while little was available on other air pollutants. The prevalence and progression of digestive diseases are influenced by multiple risk factors, such as smoking, alcohol consumption, dietary habits, obesity, and genetic predisposition [75, 76]. However, there may be an interaction or additive effect between these risk factors and the effect of air pollutants on digestive diseases, but this potential association has not been sufficiently explored. To improve the methodological quality and reproducibility of the studies, systematic reviews and meta-analyses should be conducted in accordance with the guidelines [77]. Moreover, protocols should be specified and registered in advance to ensure their transparency.

Conclusions

Based on the current evidence from meta-analyses, $PM_{2.5}$ exposure may be associated with liver dysfunction, chronic liver disease, liver cancer, and colorectal cancer, which appear to be dose-dependent. However, given the heterogeneity among primary studies and methodological limitations of the meta-analyses, these associations need to be interpreted with caution. In the future, well-designed studies are needed to explore the independent and combined effects of different air pollutants and their components on digestive diseases, and to sufficiently consider the impact of known risk factors associated with digestive diseases on the statistical results to provide more robust evidence.

Abbreviations

PM	Particulate matter
AMSTAR-2	Assessment of Multiple Meta-analyses Two
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
GROOVE	Overview Overlapping Graphical Representation
GBD	Global Burden of Disease
DALYs	Disability-adjusted life years
IBD	Inflammatory bowel disease
NAFLD	Non-alcoholic fatty liver disease
PRIOR	Preferred Reporting Items for Overviews of Reviews
MeSH	Medical Subject Heading
PEOS	Population, Exposure, Outcome, and Study design
SMD	Standardized mean difference
OR	Odds ratio
RR	Relative risk
HR	Hazard ratio
95%CI	95% Confidence interval
ICD-11	International Classification of Diseases 11th Revision
CCA	Corrected covered area
NO_X	Nitrogen oxides
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GGT	Gamma-glutamyl transferase
ROS	Reactive oxygen species
LCAT-CE	Lecithin-cholesterol acyltransferase-cholesteryl ester
CYP7A1	Cytochrome P450 family 7 subfamily A member 1
PINK1	PTEN-induced putative kinase 1
HSCs	Hepatic stellate cells
TGF-β1	Transforming growth factor-β1
DNA	Deoxyribonucleic acid
VEGF	Vascular endothelial growth factor
COX-2	Cyclooxygenase-2

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

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Authors' contributions

X.Q. and N.T. conceptualized the study; H.Z., X.Z., G.L., X.W., H.L., S.J., P.X., and X.Q. conducted the methodology; H.Z., X.Z., G.L., X.W., H.L., S.J., P.X., and X.Q. were responsible for data curation; H.Z., X.Z., Y.W., N.T., and X.Q. conducted the formal analysis.H.Z., X.Z., Y.W., P.B., X.Z., N.T., and X.Q. provided critical comments and revisions; H.Z. and X.Q. wrote the manuscript. H.Z., X.Z., G.L., X.W., Y.S., Y.W., P.B., X.Z., N.T., and X.Q. reviewed and edited the manuscript. X.Q. and N.T. supervised the study. All authors have made an intellectual contribution to the manuscript and approved the submission.

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Data availability
Data was provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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